REMARKS

No amendments have been made to the currently pending claims so a new Listing of Claims has not been provided.

In response to the office action mailed October 3, 2003, claims 1, 3-15, 18-24 and 28-29 were withdrawn; claims 2, 16-17 and 25-27 were canceled, and new claims 30-57 were added. In the amendment dated December 9, 2004, claims 30-31, 34, 37, 44-47 and 57 were amended; claims 32-33 and 35-36 were canceled; and claim 58 was added. In the amendment dated May 23, 2005, claims 30 and 57 were amended; claims 31, 34 and 58 were canceled; and claims 59-64 were newly added. Therefore, claims 30, 37-57 and 59-64 are all the claims currently pending in the present application.

The Office Action dated November 15, 2005, has been received and carefully considered. Claims 30, 37-50, 57 and 59-64 were examined on the merits. Reconsideration of the outstanding objections/rejections in the present application is respectfully requested based on the following remarks.

Election/Restriction

The Examiner states that claims 51-56 are withdrawn, as being drawn to administering neuregulin with other agents, a non-elected invention (See Restriction Requirement of 10/3/03, elected Group II, claims 2, 16-17, and 25-29, a method of using only neuregulin; irrespective that these claims were allowed 6/13/2005, since SEQ ID NO: 2 was previously deemed novel when incorrect in sequence list/CRF). In the Restriction Requirement of 10/3/03, the Examiner stated that this application contains the following inventions or groups of inventions, which are not so linked as to form a single general inventive concept;

I. Claims 1 and 3-5, drawn to a method of causing cardiomyocyte growth and/or differentiation using neuregulin (NRG), classified in class 514, subclass 2.

II. Claims 2, 16-17 and 25-29, drawn to a method of inducing remodeling of cardiac muscle cell sarcomeric and cytoskeleton structures, or cell-cell adhesions using NRG (or its derivatives), causing cardiomyocyte growth and/or differentiation, classified in class 514, subclass 2 (different process/search than Group I).

III. Claims 6-12, drawn to a method of identifying polypeptides or compounds which stimulate cardiac muscle cell differentiation using NRG and a test polypeptide or compound, classified in class 424, subclass 9.34.

IV. Claims 13-15, drawn to a method of identifying polypeptides or compounds which inhibit NRG stimulation of ventricular muscle cell differentiation, using a test polypeptide or compound, classified in class 424, subclass 9.34 (different process/search than Group III)

V. Claim 18, drawn to a method of preventing or lowering the incidence of heart disease in a mammal, comprising preventing or lowering the interference or effects of polypeptides or compounds on the action of NRG or its receptors, ErbBs, that produces heart failure, classified in class 424, subclass 1.69.

VI. Claim 19, drawn to a compound ("use of" unclear) that mimics the effects of neuregulin to treat or prevent PE, or IGF-1-mediated cardiac muscle cell dysfunction, classified in class 530, subclass 300+.

VII. Claims 20-21, drawn to a method of determining predisposition to heart disease or heart failure in a subject, comprising testing cardiac or related muscle cells of the subject for the ability to express and/or produce normal or adequate levels of neuregulin or its cognate ErbB receptors, classified in class 435, subclass 7.8.

VIII. Claims 22-23, drawn to a compound ("use of" unclear) of neuregulin, neuregulin polypeptide, neuregulin derivatives, or compounds which mimic the activities of neuregulins in the treatment or management of heart disease and heart failure in a mammal, classified in class 530, subclass 300+.

IX. Claim 24, drawn to a compound ("use of" unclear) of neuregulin, neuregulin polypeptide, neuregulin derivatives, or compounds which mimic the activities of neuregulins in the manufacture of a medicament for the treatment or management of heart disease and heart failure, classified in class 530, subclass 300+.

The Examiner stated that the inventions are distinct, each from the other because of the following reasons:

The methods (and/or compounds) in Groups I-IX are directed to different inventions, which are not connected in design, operation, and/or effect. These methods are independent since they are not disclosed as capable of use together, they have different modes of operation, they have different functions, and/or they have different effects. One would not have to practice the various methods at the same time to practice just one method alone.

The several inventions (Groups IX) above are independent and distinct, each from the other. They have acquired a separate status in the art as a separate subject for inventive effect and require independent searches. The search for each of the above inventions is not coextensive particularly with regard to the literature search. Further, a reference, which would anticipate the inventions of one group, would not necessarily anticipate or even make obvious another group. Finally, the consideration for patentability is different in each case. Thus, it would be an undue burden to examine all of the above inventions in one application. Restriction for examination purposes is therefore proper.

Applicant traverses the Examiner's withdrawal of claims 51-56. As a preliminary matter, the Applicant points out that claims 51-56 where previously allowed by the Examiner. In so doing, the Examiner has already reviewed both claims 51-56 and the other pending claims and conducted a search of the prior art. Thus, there is no undue burden on the Examiner to conduct a search for claims 51-56 in addition to a search for the other pending claims.

Additionally, claims 51-56 ultimately depend from claim 30, a method of inducing remodeling of cardiac muscle cell sarcomeric and cytoskeleton structures or cell-cell adhesions. Thus, claims 51-56 are also drawn to a method of inducing remodeling of cardiac muscle cell sarcomeric and cytoskeleton structures or cell-cell adhesions – the subject matter of Elected Group II as opposed to that of Non-Elected Groups I or III-IX.

Alternatively, Applicant traverses the Examiner's withdrawal of claims 51-56 because the Examiner has not established a *prima facie* case. Claims 51-56 are not independent from those of Group II because, as disclosed in the present application, the inventions are related and can be used together. For example, the present application teaches that:

> The present invention can be combined with current therapeutic approaches for treatment of heart failure, e.g., with ACE inhibitor treatment ACE inhibitors are angiotensin-converting enzyme inhibiting drugs which prevent the conversion of angiotensin I to angiotensin II.

Page 20, lines 16-18.

The Examiner has also not shown that the inventions have acquired a separate status in the art as a separate subject for inventive effect. See MPEP §808.02. As evidence that administering neuregulin with other agents has not developed a separate status in the art, Applicant refers the Examiner to, for example, U.S. Patent No. 6,635,249, which is on the Information Disclosure Statement submitted with this response, where claims were drawn both to neuregulin administration and neuregulin administration with other agents (*See, e.g.*, claim 1 where a neuregulin polypeptide is administered and claim 11 where neuregulin is administered during exposure to a cardiotoxic compound).

Additionally, the Examiner has not shown each subject has a separate classification or requires a different field of search. The Examiner has not cited any separate class or subclass for claims 51-56. Thus, Applicant believes it would not be an undue burden to examine all of the above inventions in one application.

Examiner Interview

The undersigned thanks the Examiner for the courtesies extended during the interviews conducted on September 7, 2005. Applicant submits concurrently herewith a summary of the Examiner Interview pursuant to MPEP 713.04.

Applicant's scheduled an interview post-allowance to inquire as to the status of a previously requested amendment to the specification, which would have corrected SEQ ID NO. 2 by substituting the corrected amino acid sequence for amino acids 177-237 of neuregulin. The Examiner indicated that the previously requested amendment had not been entered. Thus, Applicant expressed his intention to withdraw the application from issuance and file an RCE amending the sequence list/CRF to recite the correct 61 amino acid sequence. The Examiner stated that a new prior art search would need to be performed because the claims were now drawn to a protein with a different amino acid sequence.

Information Disclosure Statement

An Information Disclosure Statement and accompanying PTO-1449 form were filed with this response. There is presently no indication that the Examiner considered the documents identified in that Information Disclosure Statement. Accordingly, the Examiner is respectfully requested to acknowledge consideration of the documents identified in that Information Disclosure Statement by initialing the PTO-1449 form and returning a copy of the initialed form to the undersigned.

Claim Rejection under 35 U.S.C. § 102

Claims 30, 37-50, 57 and 59-64 stand rejected under 35 U.S.C. § 102(b) as being anticipated by WO 94/26298 (" Sklar 1") and Balligand et al. (Jan./Feb.), 1997; 3(4):351-360) ("Balligand"), and under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,444,642 B1 ("Sklar 2") and U.S. Patent No. 6,087,323 ("Gwynne").

The Examiner states that the rejection of claims 30, 37-50, 57 and 59-64 as anticipated by Sklar 1, Balligand, Sklar 2 and Gwynne are maintained for reasons of record. In the October 3, 2003 Office Action, the Examiner states that Sklar 1 teaches the use of neuregulin (and other related compounds/mimics), by contacting muscle cells (p. 3, lines 30-31), and specifically cardiac muscle cells (abstract; p. 3, line 17) and namely "any cell which contributes to muscle tissue" (p. 4, lines 17-18), in methods for normal and diseased hearts (p.8-9) for "muscle regeneration" (p. 2, col. 12) in order to induce "both the proliferation of muscle cells and the differentiation and survival of myotubes" (p. 3,

lines 15-17) and "the mitogenesis, survival, growth and differentiation of muscle cells" (p. 3, col. 26-29); wherein "[m]yogenesis . . . refers to any fusion of myoblasts to yield myotubes" [i.e. remodeling and increased cell-cell-adhesion]. The Examiner further states that Sklar 1 teaches that administration to a vertebrate, preferably a mammal (p. 4, line 5) and that "[n]euregulin effects on muscle may occur, for example, by inducing the synthesis of particular isoforms of the contractile apparatus such as the myosin heavy chain slow and fast isoforms; by promoting muscle fiber survival via the induction of synthesis of protective molecules such as, but not limited to dystrophin; and/or by increasing acetylcholine receptor molecules at the neuromuscular junction (p. 4 lines 7-16) (see also claims, including nucleic acid (gene) stimulation).

The Examiner states that Sklar 2 and Gwynne teach the same invention elements discussed above in Sklar 1. The Examiner states that Balligand teaches the use of neuregulin, as a paracrine/autocrine acting trophic factor synthesized and released by cardiac myocytes and/or endothelial cells (p. 351, 1st ¶); in cardiac endothelium and tissue growth, and specifically regulation of cardiac myocyte growth (in the developed myocardium; page 354, 2nd ¶) as well as vasculogenesis and angiogenesis, and in the function of cardiac muscle following development (abstract).

The Examiner states that Applicant argues that the references do not teach a method of using neuregulin to induce remodeling of cardiac muscle of cardiac muscle cell sarcomeric and cytoskeleton structures or cell-cell adhesions, because the references do not expressly teach the underlying bio/physiological process that neuregulin is being administered in an amount sufficient to activate the MAP kinase pathway in cardiac muscle cells (and related cascade effects). Thus, the Examiner states that U.S. Patent No. 6,162,641 ("Goldman") and U.S. Patent No. 6,750,196 ("Reh") are herein cited of record merely to indicate neuregulin's known intrinsic bio/physiological effect in cardiac cells.

Goldman is alleged to teach neuregulin's effect through the MAP kinase pathway, in a method of using neuregulin to treat muscle tissue, specifically cardiac muscle tissue (col. 7, lines 29-34), exogenously, that acts at a receptor on a cell [i.e. cardiac muscle cell] to cause a series of biochemical alterations in the MAP kinase signaling pathway/cascade within a cell [i.e. cardiac muscle cell] (col. 17, lines 38-42; Example 4, col. 33, lines 49-55). Reh is alleged to teach that neuregulins are membrane-anchored peptide growth

factors that may mediate cell-cell interactions through cell-adhesion (col. 4, lines 17-23). The Examiner alleges that since the references teach the use of neuregulin for cardiac muscle regeneration and related objectives, it is intrinsic that the underlying bio/physiological processes (i.e., cell-cell adhesion stimulation) achieving these objectives are carried out through an effective amount of neuregulin to activate the MAP kinase pathway (and similarly it is deemed intrinsic that "at least 10^{-8} M" is the base amount necessary to active said pathway); absent evidence to the contrary.

Applicant respectfully requests that the Examiner reconsider the rejection for at least the reasons stated below. Under 35 U.S.C. § 102, the Patent Office bears the burden of presenting at least a prima facie case of anticipation. *In re Sun*, 31 U.S.P.Q.2d 1451, 1453 (Fed. Cir. 1993) (unpublished). Anticipation requires that a prior art reference disclose each and every element of the claimed invention. *Id.* Rejections under 35 U.S.C. § 102 are proper only when the claimed subject matter is identically disclosed or described in the prior art. Thus, the reference must clearly and unequivocally disclose every element and recitation of the claimed invention.

Independent claims 30 and 57 state "a neuregulin protein ***consisting of*** an amino acid sequence set forth in SEQ ID NO:2." (emphasis added). The transitional phrase "consisting of" is a closed term excluding additional elements or materials not specified in the claim. Manual of Patent Examining Procedure at §211.03. SEQ ID NO:2 discloses a 61 amino acid peptide consisting of amino acids 177-237 of neuregulin. None of the cited prior art references disclose this element of the claims. Specifically, Sklar 1 and 2 do not anticipate the present invention because it discloses the use of rhGGF2 (see, Examples 1-6), which was obtained from the GGF2HBS5 clone. Sklar 1, p. 30, ln. 6; Sklar 2, Col. 15, ln. 39. The approximate size of the protein encoded by GGF2HBS5 was 423 amino acids. Sklar 1, p. 64, ln. 14; Sklar 2, Col. 31, ln. 61.

Gwynne similarly fails to anticipate the present invention because it fails to disclose "a neuregulin protein consisting of an amino acid sequence set forth in SEQ ID NO:2." Gwynne discloses the use of rhGGF2, See, Examples 1-3, Col. 25-30, which by definition includes the peptide sequences expressed by the GGF2HBS5, GGF2BPP3 and GGFHBS5 clones. See, Col. 19, lns. 16-25. The peptides encoded by those clones are

412, 257 and 423 amino acids, respectively. See, Figure 24, Figure 11D-11E, and Figure 25, respectively.

Balligand also fails to anticipate the present invention because it fails to disclose "a neuregulin protein consisting of an amino acid sequence set forth in SEQ ID NO:2." In fact, Balligand only generally refers to "neuregulin" once (other than the cumulative statement in the introduction) and discloses, at most, the probable use of neuregulin and numerous other proteins in generally regulating cardiac myocyte growth. See p. 354, Col. 2, ¶ 2.

Neither Goldman nor Reh cure the defects of these other references. Although additional references may be used to confirm the contents of an allegedly anticipating reference, the Federal Circuit has "made clear that anticipation does not permit an additional reference to supply a missing claim limitation." *See Teleflex, Inc. v. Ficosa North American Corp.*, 299 F.3d 1313, 1335, 63 U.S.P.Q.2d 1374 (Fed. Cir. 2002) (*citing, Studiengesellschaft Kohle, m.b.H. v. Dart Indus., Inc.*, 726 F.2d 724, 727, 220 U.S.P.Q. 841, 842 (Fed. Cir. 1984)). The Examiner states that Goldman and Reh are herein cited of record merely to indicate neuregulin's known intrinsic bio/physiological effect in cardiac cells. However, neither Goldman nor Reh disclose "a neuregulin protein consisting of an amino acid sequence set forth in SEQ ID NO:2."

Given the foregoing, Applicant respectfully requests that the Examiner reconsider and allow independent claims 30 and 57. Additionally, claims 37-50 and 59-64 are dependent upon independent claims 30 and 57, respectively, and should also be allowable at least by virtue of their dependency on independent claims 30 and 57. Moreover, these claims recite additional features which are not claimed, disclosed, or even suggested by the cited references taken either alone or in combination. In view of the foregoing, it is respectfully requested that the aforementioned anticipation rejection of claims 30, 37-50, 57 and 59-64 be withdrawn.

Claim Rejection under 35 U.S.C. § 103

Claims 30, 37-50, 57 and 59-64 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 94/26298 (" Sklar 1"), Balligand et al. (Jan./Feb.), 1997; 3(4):351-

360) ("Balligand"), U.S. Patent No. 6,444,642 B1 ("Sklar 2") or U.S. Patent No. 6,087,323 ("Gwynne"). Claims 30 and 57 are independent claims. Applicant respectfully requests that the Examiner reconsider the rejection for at least the reasons stated below.

As stated in MPEP §2143, to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Thus, to establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). Additionally, if an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending there from is nonobvious. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988).

As discussed above, none of the cited prior art references disclose or even suggest an element of the present claims – "a neuregulin protein ***consisting of*** an amino acid sequence set forth in SEQ ID NO:2." (emphasis added). In view of the foregoing, it is respectfully requested that the aforementioned obviousness rejection of claims 30, 37-50, 57 and 59-64 be withdrawn.

CONCLUSION

In view of the foregoing, it is respectfully submitted that the present application is in condition for allowance, and an early indication of the same is courteously solicited. The Examiner is respectfully requested to contact the undersigned by telephone at the below listed telephone number, in order to expedite resolution of any issues and to expedite passage of the present application to issue, if any comments, questions, or suggestions arise in connection with the present application.

To the extent necessary, a petition for an extension of time under 37 CFR § 1.136 is hereby made.

Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account No. 50-2613, and please credit any excess fees to the same deposit account.

Respectfully submitted,

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Dated: January 13, 2006

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